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INTERVIEW

Transitions in development – an interview with Samira Musah

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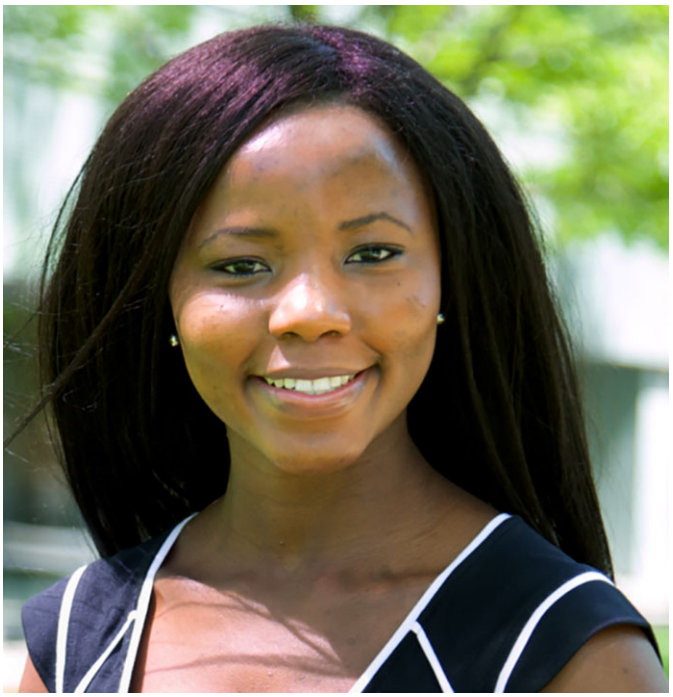
Samira Musah is an Assistant Professor in the Departments of Biomedical Engineering and Medicine at Duke University, USA. Samira's research focuses on leveraging pluripotent stem cells, bioengineering and organ-on-a-chip technologies to understand more about human kidney development, disease and therapy. We met with Samira over Microsoft Teams to hear more about her path to independence, mentors and her love of yoga.



Courtesy of Seth Kroll (Wyss Institute at Harvard, Boston, MA, USA)

Could you take me back to that moment when you became first interested in science?

As far back as I can remember, I've had an awareness of being in school and teachers talking about science, but it wasn't until I could do hands-on experiments that I really fell in love with it. One of my first memories of being excited about science was doing simple experiments at home and telling my family about them, like having a bowl of water with a mirror and a white cloth to make a rainbow. I was very lucky because I had super-enthusiastic science professors and teachers growing up, who would provide little cues encouraging me to be a scientist. I always adored my science teachers and so I gravitated towards science.

Did that encouragement lead you to want to pursue a PhD?

Frankly, I didn't understand what a PhD was until college. I happened to be in an info session for freshmen in the first semester at Binghamton University (NY, USA), where they talked about opportunities after you graduate. One of the flyers had information about the McNair Scholars Program, which is a wonderful training program for undergraduate students to have research experiences and internship opportunities. I kept the flyer because I wasn't eligible to apply that semester but, when my sophomore year came, I filled it out and submitted it to the program coordinator. She was blown away by the fact that I had made up my mind that I wanted to apply and kept the materials until I was eligible. It was through that program that I started undergraduate research.

My undergraduate advisor, Professor Omowunmi Sadik, was amazing and she is still one of my role models. It was the first time I had seen someone whose experiences I could relate to and who looked a little bit like me, doing science and excelling in it. It was fun to be in that environment and I started thinking that I could probably do research. I interacted and learned from the graduate students, postdocs and research scientists in the lab, and being there became part of my life, besides my classes. I loved the projects I worked on. I was a chemistry undergraduate student and, in the lab, we were looking at the electrochemical properties of endocrine-disrupting chemicals. We were generating derivatives of molecules to look at how they impact cellular function. I mostly did chemistry but we were also interfacing it with biology and I learned how to use chemistry to understand biological systems (Kikandi et al., 2007). Since then, I've never imagined not having a biological question involved in how I approached my chemistry – people probably think I'm more of a stem cell biologist, then they probably recognise that a lot of my approaches to stem cell biology are informed by chemistry. When it was time to apply for grad school, there was no question. Having these wonderful experiences made a lasting impression; if I had ended up in an environment where I did not like what was going on, I probably would not have thought research was a good fit for me. I feel fortunate.

You carried out your PhD studies at the University of Wisconsin with Laura Kiessling. How did you end up there?

I was at Penn State (USA) for a research opportunity the summer before I applied for graduate school and we went to Madison (University of Wisconsin, USA) for one of our symposiums where I saw the campus and met a few faculty members. I learned more about Madison and decided that I would seriously consider going there for graduate school. I loved chemistry, but I really wanted to be doing chemistry in biological systems. Laura Kiessling is an organic chemist but answers biologically relevant questions. She held joint positions in both chemistry and biochemistry, and had physical labs in both spaces so it felt like the perfect environment. When I was

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interviewing for graduate school, Laura talked to me about multiple projects in the lab. One project was designing synthetic materials and synthesising molecules to control stem cell fate decisions, which sounded cool. I had absolutely no background in stem cell biology but I was excited about learning. Laura said that I just needed enthusiasm and interest, and I would develop expertise. The rest is pretty much history.

What did you work on during your PhD?

When I started, I worked with another PhD student, Ratmir Derda, who was using phage display to discover new peptides that promoted a specific desired fate decision in human pluripotent stem cells. Initially, we were focused on molecules that promoted self-renewal without the complex animal-derived matrices (Derda et al., 2010). Later, I became interested in differentiation and biophysical control of cell fate decisions. It was at that time that Dennis Discher's group showed the impact of matrix stiffness on mesenchymal stem cell differentiation (Engler et al., 2006). I wondered what a pluripotent cell, which had not committed to any lineage, would do when presented with specific biophysical cues. That led me to start another project where I found that, even though pluripotent cells are not lineage restricted, they're selective of the mechanics of the environment. I showed that pluripotent stem cells on rigid hydrogels, specifically ones that activate the YAP signalling pathway, are more likely to remain pluripotent (Musah et al., 2012). Through that work, I made a serendipitous discovery that led to a third project: I found that matrices that inhibit YAP tended to be very good at driving neurogenesis. I wondered whether this phenomenon was purely a matrix (mechanical) property or if we could identify the exact molecular perturbations that caused the cells to become neurons (for example, YAP inhibition). For me, that was one of the most exciting discoveries from my PhD work, showing that inhibiting YAP, whether genetically, biophysically or chemically using small molecules, preferentially drives the cells to differentiate into neurons regardless of whether they're on a soft or rigid matrix (Musah et al., 2014).

You then moved to the Wyss Institute at Harvard University for your postdoc jointly supervised by Donald Ingber and George Church. What influenced your decision to go there?

I wanted to explore my interest in mechanobiology further. Don Ingber is like the god of mechanobiology so, obviously, his lab stood out to me! The more I learned about his lab, the more I realised that he was doing way more than just mechanotransduction. At the time, I was learning about what organs-on-chips were and I thought they were a cool system to probe many of these biophysical questions and how biophysics influences fate decisions in complex systems. It was even possible to add layers of complexity, such as fluid shear stress, blood flow or the movement of particles or neighbouring cells. I became interested in using some of these fundamental principles to understand disease processes. When I was interviewed, I absolutely loved the team, who were all excited about the projects that they were carrying out. I was given a lot of independence when I was a PhD student, so I felt very comfortable about going into an environment where everybody wasn't doing the same thing and I was excited to start something new. Don also gave me a lot of independence. I received the Harvard Medical School Deans postdoctoral fellowship that allowed me to work on engineered models of tissues for human disease modelling, and to look at how gene variants contribute to disease progression. George Church was, and still is, a core faculty member at the Wyss Institute; it seemed potentially natural to have both of them be my co-advisors through that fellowship program. So I ended up with two advisors, but I think it was remarkable because they also were quite complementary in terms of the skills and mentorship they provided.

What were your research interests during your postdoc?

I first worked on a project that was being led by another postdoc in the lab, which focused on engineering the bone marrow chip. I learned a lot about the design and manufacturing of microfluidic devices, and it was a nice way for me to integrate into the lab and learn about some of the ongoing projects. One such project was to build a kidney model chip. They had a nice model of the proximal tubules but, in the kidneys, we know that the glomerulus is the primary site for blood filtration. More than 90% of kidney diseases target the glomerulus so it became an essential component, but the group had not been able to make it. I learned that all the other chip models had access to commercial sources of cells, but there was no commercial, reliable source of kidney podocytes, which are the key epithelial cell type in the glomerulus – it would require a highly invasive procedure to try to get these cells from volunteers. The key metric for organ chip success is an ability to model organ-level functions, so the lack of podocytes and a functional glomerulus became a huge limitation. I wondered if we could generate these critical cells from stem cells. I started by learning about how the kidney develops, and I had a plan for how I might at least try directing podocyte differentiation from stem cells. Of course, the first try didn't quite work, but I continued optimising and by the second or third round of experiments, I pretty much had the protocol that my lab continues to use (Musah et al., 2017, 2018; Burt et al., 2020). We now have an unlimited supply of cells that we can generate on demand and use to model human kidney function and disease phenotypes, as well as toxicity trials and mechanistic studies (Roye et al., 2021; Burt et al., 2021; Bonner et al., 2022; Kalejaiye et al., 2022; Mou et al., 2022; Roye and Musah, 2022).

When did you decide to apply for independent positions?

My graduate student advisor was very hands-off, so I had to make a lot of my own decisions. Initially, that was challenging but, as I became more experienced, I appreciated that approach a lot. I had a great deal of independence to design, execute and troubleshoot a project, and I realised that I needed these experiences to run a successful lab. As a postdoc, I learned how to extend in different directions and how to work with people from completely different fields. It really gave me a whole new level of understanding of how to think about problems and design projects. Once my work on podocyte differentiation and reconstitution of glomerular function was published, I felt a lot more confident and ready to extend my experiences and skills. It was around that time that I started applying for faculty positions.

How did you decide where to apply and which position to accept?

First of all, I was excited by an environment where I felt like I could interface with not just biological aspects, but also medical aspects – where I could have clinicians as colleagues and maximise that expertise to translate technologies into the clinic. I felt it would be much more natural to start collaborations in a close environment. It became a deal breaker if a university didn't have a medical school nearby. Both of my postdoc advisors were very candid; they told me what I needed to know and not just what they thought I wanted to hear. They told me what to look for at universities, that I should make sure that I could do my science, but also think about whether

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I would love to live there, and enjoy coming to work and interacting with colleagues. When I was a postdoc at Harvard, one piece of advice I got through the Harvard Medical School Dean's fellowship program was to have a mentor outside Harvard. I was fortunate to also be part of the Keystone fellowship program and my mentor, Geoff Ginsburg, is a Duke faculty member who was absolutely amazing. He obviously loves being at Duke, so he was definitely part of the reason why I felt very comfortable moving here. Of course, George Church also went to Duke and he still loves it. Just about everybody I've met has said great things about the environment at Duke. When I was interviewed in the fall, it was beautiful and I really fell in love with the environment – I feel that it contributes to my quality of life.

What was going through your mind when you first became a group leader at Duke University?

Quite honestly, it was exciting. I didn't even pause to think that I was supposed to be terrified until I talked to other people. I had a blank slate to build a lab exactly the way I envisioned. For me, that was empowering and liberating. Once I started running the lab, I realised the gaps in my experiences and knowledge. I was doing a lot of important work in addition to science and I was shocked by how much time those other responsibilities required. That was probably the most challenging aspect of my faculty position. I still have to figure out how to manage these other responsibilities and still dedicate precious time to science, which is really the reason I'm here.

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How did you go about hiring people to join your group?

The very first PhD student I recruited in my lab, Morgan Burt, was a technician back in Boston where I was a postdoc. She's on track to graduate in a couple of months, which is exciting! Morgan was interested in, and curious about, what I was doing in Boston. When I communicated to my colleagues that I was seriously thinking of coming to Duke, she said she would come with me. I thought she was crazy because, as a new faculty member, it would probably be the end of her first or second semester by the time the lab was set up. But she was driven and clearly not terrified by the idea of starting something new. It's rare to find students with that openness and confidence that they would do well. I really admire her and she's done remarkably well. Since I recruited Morgan, I've involved her (and everybody else in the lab) in deciding who else to hire. Usually, we're on the same page when interviewing people, but there are times when my group members pointed out things that made me change my mind about some candidates. I found involving my team very important and we've been fortunate that this approach has served us well.

What advice would you give to people starting their own labs?

One of the things I learned during COVID is that it's important to have students think more about what they're going to do before they do it, for them to write why they're doing something and to be able to make a compelling case. Make sure that students understand that you just don't go in the lab and run the next cool experiment or design an experiment purely based on a technique you want to learn. Rather, let the questions drive the project design. In their first year, especially the first semester, I invest more time with students to help them develop those skills. Once they get the fundamentals, they're able to become independent scientists and take things in directions that I haven't thought about or seriously considered.

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Could you summarise the research themes of your lab at the moment?

We look at how molecular or biophysical cues control tissue development to build more complex systems that could be useful for understanding human biology, disease processes and therapeutic platforms. We have projects aimed at the directed differentiation of stem cells into organ-specific cell types. We hope to discover mechanisms that could be applied to human development using these methods. There are some diseases that develop and progress very differently in humans than in animals. We specifically look at kidney disease, which doesn't develop the same way in mice as in humans, so many of the mechanisms that are discovered in mice don't extrapolate to humans. We hope that the technologies we build help to bridge this gap. In addition, there are no effective diagnostic tools for early kidney disease; by the time it's diagnosed in the clinic, it's usually irreversible. I hope that some of these technologies help to discover new biomarkers and therapeutics for kidney disease diagnosis and treatment. Some recent projects have yielded some exciting results in that direction (Burt et al., 2021; Kalejaiye et al., 2022). We're also an organ engineering lab, so we hope that we can advance this technology to start building artificial organs or, at least, functional units of the kidneys that could replace some functional loss in patients. A final direction is focused on injury repair and tissue regeneration.

You've received many awards and distinctions during your career; which of them has been the most important to you?

They are all important because, behind each award, there's a unique story that the award has either recognised or enabled. All of these stories have shaped who I am and what I do. As an ambitious scientist, I always think maybe the next one will be the most important.

At any point have you considered a non-academic career?

I've always dreamt of building a yoga studio. In my second year of graduate school, a more senior graduate student in another fellowship program invited me to go to Bikram yoga. It was so hot; I couldn't believe how people were doing the positions – it just blew my mind. But I fell in love with yoga. It's truly become part of who I am and how I live. I seriously thought about taking the yoga certification class as a graduate student. At this point in my career, if I wanted to do something else, I would love to do something along those lines.

Is there anything that Development readers would be surprised to learn about you?

I am absolutely terrified of lab animals! When I took the human embryonic stem cell culture training course, I couldn't believe that they had us dissect the mouse embryos ourselves and isolate the mouse embryonic fibroblast feeder cells. I had to get the instructor

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to take the embryos out and then I did the digestion and isolation. I might collapse if I had to touch the mouse – and especially get embryos out of it. Unsurprisingly, we don't do much animal work now! I am also not a fan of avocados. My husband thinks that's very odd, so I thought I would share that!

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